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Global Research & Development

April 11, 2005

Division of Dockets Management Branch (HFA-305)
Food and Drug Administration
5630 Fishers Lane, rm. 1061
Rockville, Maryland 20852

Re: Draft Guidance for Industry on Clinical Lactation Studies—Study Design, Data Analysis, and Recommendations for Labeling
[Docket No. 2005D-0030, 70 *Federal Register*, 6697, February 8, 2005]

Dear Dockets Management,

Pfizer Inc submits these comments on the Draft Guidance for Industry on Clinical Lactation Studies – Study Design, Data Analysis, and Recommendations for Labeling published in the *Federal Register* on February 8, 2005.

We thank you for this opportunity to comment and would invite direct dialogue with the Agency if you would consider the opportunity valuable.

Sincerely,

Melissa S Tassinari

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2005D-0030

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General Comments:

There has been little formal assessment of drug entry into breast milk, as is pointed out in the draft guidance. It is important to provide clear and accurate information on potential impact of drug exposure on lactation and we agree that 'consistent application of adequate study designs' yielding such data would be of benefit to lactating women and their health care providers. [Lines 131-133].

The central issue, not clearly stated in this document, is when drug clearance into breast milk might be a significant clinical issue, and thus require pharmacokinetic assessment. Also, it is not clear from this guidance whether there is an expectation that lactation studies would be required for approval, or might be optional. We suggest that the principal aim of clinical lactation studies should be to address any potential effects of lactation on the PK/PD of the women taking the drug, the effects of the drug on milk production and composition and the potential risk of drug transfer via breast milk. Studies to address these objectives are not the most appropriate designs to assess potential impact on the infant and should be used as triggers for more work only in those cases where it is clear that a significant exposure would occur. The level of drug exposure in milk that would trigger pharmacokinetic studies in the breast fed child should be defined. As noted in the guidance [lines 74-76] presence of a drug in the breast milk does not necessarily indicate a health risk for the breast fed child.

While it is clear that certain drugs are excreted in breast milk, there is no consistent evidence that this additional route of clearance has led to therapeutic failure in the mother, and evidence of toxicity in neonates and young children due to drug exposure in breast milk are limited to case reports.

The potentially problematic drugs are lipophilic weak bases, PCBs or PBBs, or compounds that undergo active transport into milk. This perspective should be provided as part of the guidance. The guidance should focus on in vivo studies for those compounds that are lipophilic weak bases or may undergo some active transport at the level of the mammary gland (suggested by susceptibility to active transport somewhere else in the body), rather than any drug that might be used in women of reproductive age.

The range and extent of assessments suggested appear to be elaborate, given the absence of clearly defined clinical risks. In some cases, the assessments are impractical (e.g. trying to get the time course of drug concentrations and/or drug pharmacodynamics in a baby of <6months, or validation of unique assays (e.g. in tears; lines 408-410). Children are most at risk of drug effects in the early postnatal period; most drug metabolizing enzymes mature rapidly after birth. Therefore, serial assessment of PK in infants in longitudinal studies should not be recommended.

We suggest that the draft guidance provide a stepwise approach to the conduct of clinical lactation studies: e.g. for compounds with characteristics where assessment **might** be appropriate; to perform simultaneous plasma and milk assessment in the mother only (IV.B.1); in cases where **appreciable** drug excretion in breast milk is demonstrated, to potentially assess exposure in the breast fed child. The difficulty and complexity of simultaneous PK assessment of mother-infant pairs realistically makes this an unlikely option and we suggest that this should not be listed as the first assessment example.

Specific Comments:

I. Introduction

Line 32: Suggest deletion of this bullet. If determination of the effects of exposure for a particular drug in breast-fed infants is needed, then more targeted studies in the infant should be designed. This should not be a trigger for a clinical lactation study.

III. Considerations For When To Conduct A Clinical Lactation Study

Lines 142, 147, and 150: The term "women of childbearing potential" might be more appropriate, than the term "women of reproductive age" as there are examples of drugs that have reproductive toxicology issues, where their use is restricted in women of childbearing potential but not in sterilized women of reproductive age (e.g. atorvastatin).

Lines 171-174. We disagree with the statement that models of M/P do not help. M/P ratios predicted from in vitro data and/or physicochemical characteristics and a consideration of active transport should allow one to select those drugs that are of specific concern that should be studied in vivo. If this type of information is available it should be used along with the information on anticipated use of the drug, particularly for study design.

IV. Study Design Considerations

Lines 207-239. Mother-Infant Pair design. As noted above this option should not be considered first line testing but should be considered only after studies done in lactating women alone and only if significant presence of the drug in breast milk raises concern for significant exposure to the breast-fed infant.

Line 213: It may be difficult to quantify the effects of drugs on milk production given small sample sizes, and the possible confounding influence of external non-pharmacological factors. In general there is a clear pharmacological rationale for those drugs shown to affect milk production (estrogens, dopamine agonists and antagonists).

Lines 268-287: Lactating Women (Milk Only). The rationale for "milk only" studies is unclear. Obtaining PK data in milk in the absence of corresponding PK data makes it difficult to achieve the objectives stated in this section.

Line 289: C. Other Design Considerations. For most drugs, assessments of drug levels in milk at various times in the lactation process is not necessary, as the amount of drug in milk does not provide a significant dose to the child under any conditions. Therefore, the longitudinal and multiple arm studies should rarely, if ever, be considered.

Lines 341-352. Controls. Comparisons of PK in lactating versus nonlactating women are not a major consideration. The document should describe what potential physiologic processes would affect drug disposition in the mother. If one is concerned about major differences in PK, these can be assessed using historical controls. It is not necessary to assess PK in the mother after weaning is complete, nor is the use of control; non-lactating volunteers likely to yield much useful information.

Lines 379-89. Sample Collection and Analysis. Milk samples at a certain collection time, i.e. x hours after dosing could be combined from both breasts. However, collection intervals analogous to urine collection intervals (e.g. the 4-8 hours dosing used in the guidance example) and pooling of samples collected at different times should never be used. Milk is stored in highly vascular alveoli, where there is ample opportunity for bi-directional movement of drug between milk and plasma. This is the entire basis for the calculation of the M/P ratio. Thus milk concentrations represent an instantaneous or nearly instantaneous reflection of drug content, not the time averaged excretion of drug represented by a sample of urine that has been collecting in the bladder over a number of hours.

Lines 495-500. The table on page 12 should reflect the appropriate analysis, focusing on AUC in milk over an interval rather than the collection interval analysis.